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10/535,312	06/05/2006	Sung Youb Jung	Q115522	5682

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
02/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/535,312	JUNG ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8,9,11-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,9,11-13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/5/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-6, 8, 9, 11-13, 15 and 16 are all the pending claims for this application.

2. Claims 1 and 12 were amended in the Response of 2/4/10.

3. Claim 15 is withdrawn from examination.

4. Claims 1-6, 8, 9, 11-13 and 16 are all the pending claims under examination.

5. Finality of the Office Action of 12/4/09 is withdrawn under MPEP 609.04(b) in view of the IDS filed 1/5/10.

6. This Office Action contains new grounds for rejection in view of Applicants amendment of the claims and the IDS of 1/5/10. This Office Action is final.

Information Disclosure Statement

7. The information disclosure statement (IDS) submitted on 1/5/10 was filed after the mailing date of the final Office Action on 12/4/09. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. The initialed and signed 1449 form is attached.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. The rejection of Claims 1-6, 8 and 16 under 35 U.S.C. 103(a) as being unpatentable over Kitai et al. (Appl. Microbiol. Biotechnol 28(1):52-56 (Mar. 1988); cited in the IDS of 10/9/09) in view of Simmons et al. (Nat. Biotech. 14:629-634 (1996)) and further in view of Sytkowski et al. (WO 99/02709; published 1/21/99); cited in the IDS of 10/9/09) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 12/4/09 as follows:

"Claims 1-6, 8 and 16 are interpreted as being drawn to a method for producing a Ig Fc in the cytoplasm or secreted from an E coli having been transfected with a nucleotide encoding the STII signal sequence and the Ig Fc domain without a variable domain (Claim 1), where the Ig Fc region is from IgG, IgA, IgM, IgE or IgD, (Claim 2) or for the subtypes IgG1, IgG2, IgG3 and IgG4 (Claim 3), or IgG4 (Claim 4), where the Fc of Claim 4 is aglycosylated (Claim 5), and Fc comprises a portion of a hinge (Claim 6 and 16), and where the Fc is from a heavy or light chain (Claim 8).

It would have been prima facie obvious to have produced the instant claimed method for producing soluble Ig Fc domains from an E. coli in view of Kitai, Simmons and Sytkowski.

Kitai discloses a penicillinase signal peptide and hIgG-Fc were fused through the one additional amino acid, Ser. This hybrid protein was translocated "across the inner membrane, correctly processed between Ala and Set, and excreted into the culture medium in the dimeric form. These results indicate that this penicillinase signal peptide works efficiently, even when a foreign protein is fused. Kitai discloses plasmid pEAP8 was an excretion vector in *E. coli* transformants (Kate e tal. 1987) and containing the DNA region needed for the extracellular production in E. coli, that is KII gene of pMB9, Ex promoter.and penicillinase promoter-signal-peptide. Kitai does not teach using the heat-stable enterotoxin signal peptide or the constant regions from IgA, IgM, IgE or IgD, or for the subtypes IgG1, IgG2, IgG3 and IgG4 whereas do Simmons and Sytkowski.

Simmons discloses examples of three heat stable enterotoxin (STII) signal sequence derivatives differing only in the TIR and maintaining the wildtype amino acid sequence (Table 1, variants 1, 4, 6) which improved the secretion of a sample of heterologous proteins over wildtype STII constructs in *E coli* transformants. Simmons compared expression of a heterologous gene of interest inserted downstream of the phoA promoter, trp Shine-Delgarno and an STII signal sequence possessing a different relative TIR strength. Simmons teaches the optimal level of protein synthesis needs to be determined empirically for every heterologous protein and the panel of vectors with differing translational strengths provides a means by which to readily adjust this factor. Simmons appreciates

producing heterologous proteins using the STII signal sequence but does not suggest the heterologous protein is the constant regions from IgA, IgM, IgE or IgD, or for the subtypes IgG1, IgG2, IgG3 and IgG4 whereas does Sytkowski. The IgG of Kitai would also be considered a heterologous protein with respect to the E. coli host expression system.

Sytkowski teaches cloning Fc domains from IgGl, IgG2, IgG2a, IgG3, IgG4, IgM, IgA, IgD or IgE of the heavy or light chain, where the Ig constant region comprises immunoglobulin hinge region, CH2 domain and CH3 domain or CL1 domain, respectively. Sytkowski teaches the entire immunoglobulin heavy chain constant region (CHI-hinge-CH2-CH3) or alternatively, the immunoglobulin constant region can comprise all, or a portion of the hinge region, the CH2 domain and the CH3 domain. The immunoglobulin constant region can also comprise the CL1 domain of an immunoglobulin light chain. Finally Simmons teaches a fusion protein may comprise a signal or targeting sequence (p. 5). The proteins of Sytkowski use the cloned Fc domains to create a fusion protein with cloned EPO, however, it is the examiner's position that the EPO portion is not important or essential and can be removed from the Sytkowski art reference method in setting forth this obviousness rejection, see Eisai Co. v. Dr. Reddy's Laboratories, 533 F.3d 1353, 1358 (Fed. Cir. 2008) (noting in regard to obviousness, that the record provided no reason to start with a lead compound and then drop the feature of the lead compound that leads to its advantageous properties) (cited at page 3 of the Reply Br.). The ordinary artisan would not have considered the EPO portion an essential element, such that its removal would render the method of Sytkowski inoperable. This is supported by the implied statements of Sytkowski that the Ig constant domain alone binds the Fc receptor or can have ADCC or ACC activity or extends the half-life of a molecule to which it is attached (p. 15), and thus to produce an isolated Fc would have advantages for other uses other than fusing it to EPO.

The ordinary artisan would have been motivated and reasonably assured of success in having produced the instant claimed method in view of Kitai, Simmons and Sytkowski. The references alone address the expression of cloned proteins in E. coli systems where Kitai and Simmons use different but otherwise interchangeable signal sequences and replacing the penicillinase sequence with the STII sequence of Simmons would seemingly improve the product outcome in E. coli cytosol as well as secreted proteins. To have considered expressing an Fc protein was contemplated and reduced to practice by Kitai and therefore obvious, and further where Simmons appreciates using the STII to express many different heterologous proteins in E. coli, where contiguous or portions of Fc domains including portions of the hinge from different antibody isotypes and isoforms were contemplated by Sytkowski in a fusion protein format. The ordinary artisan would have appreciated that human proteins expressed in E. coli would not be glycosylated, so that an Fc from IgG4 would have been aglycosylated using the claimed method. The ordinary artisan would have been assured of success because the level of skill and technology and the reagents for producing isolated Fc's was already reduced to practice as set forth in the three references where in order to obtain an abundance of purified Fc proteins absent further manipulation than fusing the Fc to an STII sequence, the ordinary artisan could have predicted a reasonably achievable outcome."

Applicants allegations on pp. 7-9 of the Response of 2/4/10 and the amendment of Claim 1 to recite that the "the immunoglobulin constant region is expressed in the cytoplasm in a water soluble form and is not secreted into the medium" has been considered and is not found persuasive. Applicants allege the amended claims to introduce the new limitation obviate the rejection because neither Kitai alone or in combination teaches a method to produce a Fc region into a cytoplasm of a host transformant.

Response to Arguments

It is the examiner's opinion that the method would still have been obvious over Kitai, Simmons and Sytkowski despite the introduction of the new limitation.

Kitai teaches expression promoting plasmids for use in E. coli.

Simmons teaches that the optimal level of protein synthesis needs to be determined empirically for every heterologous protein and the panel of vectors with differing translational strengths provides a means by which to readily adjust this factor. Simmons teaches "the efficient transport of many heterologous proteins across a membrane is dependent upon the coupling of translation with translocation. The optimization of translational levels may represent the optimization of this coupling". Thus a reasonable conclusion to be drawn from Simmons is that absent efficient translation, enough of the heterologous protein would not be expected to be secreted into the medium and would otherwise be retained in the cytoplasm or periplasmic space. Simmons recognizes that the extent to which any heterologous protein is secreted depends on the particular construct, and Simmons teaches examples of constructs that are poor secreters. Thus the references teach examples of secreting and non-secreting constructs (see Figure 1 and Table 1) and the latter of which are encompassed by the instant claimed method.

Finally, in response to applicant's arguments against the Kitai reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The rejection is maintained.

9. The rejection of Claims 1, 9 and 12 under 35 U.S.C. 103(a) as being unpatentable over Kitai et al. (Appl. Microbiol. Biotechnol 28(1):52-56 (Mar. 1988); cited in the IDS of 10/9/09) in view of Simmons et al. (Nat. Biotech. 14:629-634 (1996)) and further in view of Sytkowski et al. (WO 99/02709; published 1/21/99); cited in the IDS of 10/9/09) as applied to claim 1 above, and further in view of Lilly (US 20040053370; filed 5/29/03) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 12/4/09 as follows:

"The interpretation of Claim 1 is discussed above under section 10. Claims 9 and 12 are drawn to the Fc isotype for IgG4 of SEQ ID NO:29.

Lilly teaches an Fc sequence having 100% identity to SEQ ID NO 29 of Claims 9 and 12 (see attached sequence search alignment) and used to construct fusion proteins. Lilly teaches "[0238] Based on these studies, Fc regions can be modified at the catabolic site to optimize the half-life of the fusion proteins. It is preferable that the Fc region…be derived from an IgG1 or an IgG4 Fc region…and even more preferable that the Fc region be IgG4or derived from IgG4. Preferably the IgG Fc region contains both the CH2 and CH3 regions including the hinge region. Thus in view of Kitai, Simmons and Sytkowski, the ordinary artisan would have found motivation use the IgG4 Fc of Lilly in the construct of Kitai in view of Simmons and Sytkowski where according to Lilly the IgG4 Fc is preferable.

Applicants allegations on pp. 7-9 of the Response of 2/4/10 and the amendment of Claim 1 to recite that the "the immunoglobulin constant region is expressed in the cytoplasm in a water soluble form and is not secreted into the medium" has been considered and is not found persuasive. Applicants allege the amended claims to introduce the new limitation obviate the rejection because neither Kitai alone or in combination teaches a method to produce a Fc region into a cytoplasm of a host transformant.

Response to Arguments

It is the examiner's opinion that the method would still have been obvious over Kitai, Simmons, Sytkowski and Lilly despite the introduction of the new limitation.

Kitai teaches expression promoting plasmids for use in E. coli. Simmons teaches that the optimal level of protein synthesis needs to be determined empirically for every heterologous protein and the panel of vectors with differing translational strengths provides a means by which to readily adjust this factor. Simmons teaches "the efficient transport of many heterologous proteins across a membrane is dependent upon the coupling of translation with translocation. The optimization of translational levels may represent the optimization of this coupling". Thus a reasonable conclusion to be drawn from Simmons is that absent efficient translation, enough of the heterologous protein would not be expected to be secreted into the medium and would otherwise be retained in the cytoplasm or periplasmic space. Simmons recognizes that the extent to which any heterologous protein is secreted depends on the particular construct, and Simmons teaches examples of constructs that are poor secreters. Thus the reference teach examples of secreting and non-secreting constructs (see Figure 1 and Table 1) and the latter of which are encompassed by the instant claimed method.

Finally, in response to applicant's arguments against the Kitai reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The rejection is maintained.

10. The rejection of Claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Kitai et al. (Appl. Microbiol. Biotechnol 28(1):52-56 (Mar. 1988); cited in the IDS of 10/9/09) in view of Simmons et al. (Nat. Biotech. 14:629-634 (1996)) and further in view of Sytkowski et al. (WO 99/02709; published 1/21/99); cited in the IDS of 10/9/09) as applied to claim 1 above, and further in view of Kwon et al. (WO200015661; published 3/23/00) is maintained.

For purposes of review, the rejection was set forth in the Office Action of 12/4/09 as follows:

"The interpretation of Claim 1 is discussed above under section 10. Claim 11 is drawn to the heat stable enterotxin signal sequence of SEQ ID NO: 36, 37, 38, 40, 41, 42, 43, 44, 45, or 46.

Kwon teaches heat stable enterotoxin II signal sequence having 100% identity to SEQ ID NO: 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 and 46 of Claim 11 (see attached sequence search alignments) and used to construct fusion proteins. Kwon teaches the modified signal sequences enhance the efficiency of peptide secretion from the E. coli cells, and the modified signal peptides may be used according to standard recombinant DNA methodolgies to direct the secretion of peptides from microorganisms (Abstract). Thus in view of Kitai, Simmons and Sytkowski, the ordinary artisan would have found motivation to use the modified signal peptide sequences of Kwon in the construct of Kitai in view of Simmons and Sytkowski where the ordinary artisan would be reasonably assured that the signal peptides would have enhanced the secretion of Fc."

Applicants allegations on pp. 7-9 of the Response of 2/4/10 and the amendment of Claim 1 to recite that the "the immunoglobulin constant region is expressed in the cytoplasm in a water soluble form and is not secreted into the medium" has been considered and is not found persuasive. Applicants allege the amended claims to introduce the new limitation obviate the rejection because neither Kitai alone or in combination teaches a method to produce a Fc region into a cytoplasm of a host transformant.

Response to Arguments

It is the examiner's opinion that the method would still have been obvious over Kitai, Simmons, Sytkowski and Kwon despite the introduction of the new limitation.

Kitai teaches expression promoting plasmids for use in E. coli.

Simmons teaches that the optimal level of protein synthesis needs to be determined empirically for every heterologous protein and the panel of vectors with differing translational strengths provides a means by which to readily adjust this factor. Simmons teaches "the efficient transport of many heterologous proteins across a membrane is dependent upon the coupling of translation with translocation. The optimization of translational levels may represent the optimization of this coupling". Thus a reasonable conclusion to be drawn from Simmons is that absent efficient translation, enough of the heterologous protein would not be expected to be secreted into the medium and would otherwise be retained in the cytoplasm or periplasmic space. Simmons recognizes that the extent to which any heterologous protein is secreted depends on the particular construct, and Simmons teaches examples of constructs that are poor secreters. Thus the reference teaches examples of secreting and non-secreting constructs (see Figure 1 and Table 1) and the latter of which are encompassed by the instant claimed method.

Finally, in response to applicant's arguments against the Kitai reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The rejection is maintained.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

11. Claims 1-6, 8, 9, 11-13 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6, 8, 9, 11-13 and 16 are interpreted as being drawn to a method where an immunoglobulin constant region is... "not secreted into the medium."

The specification on p. 26 at lines 25- p. 27, line 9 teaches:

"The immunoglobulin constant region fused to a signal sequence according to the present invention, expressed in a prokaryotic cell according to the above method, was surprisingly not expressed in the periplasmic space but was overexpressed in a water-soluble form in the cytoplasm, and the signal sequence was accurately processed. In the detailed practice of the present invention, the amount of the fusion protein secreted into the medium or periplasmic space was negligible. When cells were disrupted and subjected to Western blotting, proteins were overexpressed in the cytoplasm in a water-soluble form."

The specification specifically teaches that the proteins are *not* secreted into the medium or the periplasmic space, but the negative proviso only excludes the medium. Thus rather than claiming that the protein is expressed in soluble form in the cytoplasm,

the new limitation encompasses protein expression occurring anywhere in the cell but for expressing it into the medium, when the specification teaches the contrary.

The use of a negative limitation is used to define the invention in terms of what it is not, rather than distinctly and particularly claiming a specific location or localization that meet the claim requirements and that is supported (and enabled) in the specification. Under MPEP 2173.05(i) "Any negative limitation or exclusionary proviso must have basis in the original disclosure."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1-6, 8 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrews et al. (Gene 182:101-109 (1996); cited in the IDS of 1/5/10) in view of Simmons et al. (Nat. Biotech. 14:629-634 (1996); cited in the PTO 892 form of 12/4/09)

and further in view of Sytkowski et al. (WO 99/02709; published 1/21/99); cited in the IDS of 10/9/09).

Claims 1-6, 8 and 16 are interpreted as being drawn to a method for producing a Ig Fc that is soluble and is not secreted into the medium from an E coli having been transfected with a nucleotide encoding the STII signal sequence and the Ig Fc domain without a variable domain (Claim 1), where the Ig Fc region is from IgG, IgA, IgM, IgE or IgD, (Claim 2) or for the subtypes IgG1, IgG2, IgG3 and IgG4 (Claim 3), or IgG4 (Claim 4), where the Fc of Claim 4 is aglycosylated (Claim 5), and Fc comprises a portion of a hinge (Claim 6 and 16), and where the Fc is from a heavy or light chain (Claim 8). The negative proviso is interpreted as meaning that the protein is secreted in the cytoplasm.

It would have been prima facie obvious to have produced the instant claimed method for producing soluble Ig Fc domains from an E. coli in view of Andrews, Simmons and Sytkowski.

Andrews discloses the expression of a polypeptide in E. coli, using the STII signal sequence leading to cytoplasmic expression (pp. 104-105):

"The STII leader is expected to facilitate transport of V135.3 to the periplasm and thus expedite the facile purification of VI35.3 following osmotic shock. In addi\- tion, the potential folding of V[35.3 which contains two cysteine residues might be expedited in the more oxidizing environment of the periplasmic space, relative to the cytosol. However, we found that V135.3 expressed from all vectors was localized in the cytosol despite the presence of the STII leader sequence in the constructs. Furthermore, amino acid sequence analysis showed that even without translocation of V135.3 to the periplasm, the leader peptide had been cleaved off correctly.",

and on p. 106, Col.2:

"Irrespective of its localization, a statistical model based on amino acid composition (Wilkinson and Harrison, 1991) predicts a 95% probability of V135.3 being insoluble when expressed in E. coli."

Andrews does not teach using the heat-stable enterotoxin signal peptide resulting in a soluble protein or the constant regions from IgA, IgM, IgE or IgD, or for the subtypes IgG1, IgG2, IgG3 and IgG4 whereas do Simmons and Sytkowski.

Simmons discloses examples of three heat stable enterotoxin (STII) signal sequence derivatives differing only in the TIR and maintaining the wildtype amino acid sequence (Table 1, variants 1, 4, 6) which improved the secretion of a sample of heterologous proteins over wildtype STII constructs in *E coli* transformants. Simmons compared expression of a heterologous gene of interest inserted downstream of the phoA promoter, trp Shine-Delgarno and an STII signal sequence possessing a different relative TIR strength. Simmons teaches the optimal level of protein synthesis needs to be determined empirically for every heterologous protein and the panel of vectors with differing translational strengths provides a means by which to readily adjust this factor.

Simmons teaches "the efficient transport of many heterologous proteins across a membrane is dependent upon the coupling of translation with translocation. The optimization of translational levels may represent the optimization of this coupling". Thus a reasonable conclusion to be drawn from Simmons is that absent efficient translation, enough of the heterologous protein would not be expected to be secreted into the medium and would otherwise be retained in the cytoplasm or periplasmic space. Simmons recognizes that the extent to which any heterologous protein is secreted depends on the particular construct, and Simmons teaches examples of constructs that

are poor secreters. Thus the reference teaches examples of secreting and non-secreting constructs (see Figure 1 and Table 1) and the latter of which are encompassed by the instant claimed method.

Simmons appreciates producing heterologous proteins using the STII signal sequence but does not suggest the heterologous protein is the constant regions from IgA, IgM, IgE or IgD, or for the subtypes IgG1, IgG2, IgG3 and IgG4 whereas does Sytkowski.

Sytkowski teaches cloning Fc domains from IgGl, IgG2, IgG2a, IgG3, IgG4, IgM, IgA, IgD or IgE of the heavy or light chain, where the Ig constant region comprises immunoglobulin hinge region, CH2 domain and CH3 domain or CL1 domain, respectively. Sytkowski teaches the entire immunoglobulin heavy chain constant region (CHl-hinge-CH2-CH3) or alternatively, the immunoglobulin constant region can comprise all, or a portion of the hinge region, the CH2 domain and the CH3 domain. The immunoglobulin constant region can also comprise the CL1 domain of an immunoglobulin light chain. Finally Simmons teaches a fusion protein may comprise a signal or targeting sequence (p. 5). The proteins of Sytkowski use the cloned Fc domains to create a fusion protein with cloned EPO, however, it is the examiner's position that the EPO portion is not important or essential and can be removed from the Sytkowski art reference method in setting forth this obviousness rejection (see *Eisai Co. v. Dr. Reddy's Laboratories*, 533 F.3d 1353, 1358 (Fed. Cir. 2008) (noting in regard to obviousness, that the record provided no reason to start with a lead compound and then drop the feature of the lead compound that leads to its advantageous properties) (cited

at page 3 of the Reply Br.). The ordinary artisan would not have considered the EPO portion an essential element, such that its removal would render the method of Sytkowski inoperable. This is supported by the implied statements of Sytkowski that the Ig constant domain alone binds the Fc receptor or can have ADCC or ACC activity or extends the half-life of a molecule to which it is attached (p. 15), and thus to produce an isolated Fc would have advantages for other uses other than fusing it to EPO.

The ordinary artisan would have been motivated and reasonably assured of success in having produced the instant claimed method in view of Andrews, Simmons and Sytkowski. The references alone address the expression of cloned proteins in E. coli systems where Andrews and Simmons use different but otherwise interchangeable STII signal sequences and replacing the Andrews sequence that does not produce soluble proteins with the STII sequence of Simmons would seemingly improve the product outcome in E. coli cytosol as well as secreted proteins, e.g., periplasm. To have considered expressing an heterologous protein was contemplated by Andrews (p. 108) and therefore obvious further where Simmons appreciates using the STII to express many different heterologous proteins in E. coli, and where contiguous or portions of Fc domains including portions of the hinge from different antibody isotypes and isoforms were contemplated by Sytkowski in a fusion protein format. The ordinary artisan would have appreciated that human proteins expressed in E. coli would not be glycosylated, so that an Fc from IgG4 would have been aglycosylated using the claimed method. The ordinary artisan would have been assured of success because the level of skill and technology and the reagents for producing isolated Fc's was already reduced to practice

as set forth in the Sytkowski reference where in order to obtain an abundance of purified Fc proteins absent further manipulation than fusing the Fc to an STII sequence, the ordinary artisan could have predicted a reasonably achievable outcome.

13. Claims 1, 9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrews et al. (Gene 182:101-109 (1996); cited in the IDS of 1/5/10) in view of Simmons et al. (Nat. Biotech. 14:629-634 (1996); cited in the PTO 892 form of 12/4/09) and further in view of Sytkowski et al. (WO 99/02709; published 1/21/99); cited in the IDS of 10/9/09) as applied to claim 1 above, and further in view of Lilly (US 20040053370; filed 5/29/03); cited in the Office Action of 12/4/09).

Claims 9 and 12 are drawn to the Fc isotype for IgG4 of SEQ ID NO:29.

Lilly teaches an Fc sequence having 100% identity to SEQ ID NO 29 of Claims 9 and 12 (see sequence search alignment in the PTO 892 form of 12/4/09) and used to construct fusion proteins. Lilly teaches "[0238] Based on these studies, Fc regions can be modified at the catabolic site to optimize the half-life of the fusion proteins. It is preferable that the Fc region…be derived from an IgG1 or an IgG4 Fc region…and even more preferable that the Fc region be IgG4or derived from IgG4. Preferably the IgG Fc region contains both the CH2 and CH3 regions including the hinge region. Thus in view of Andrews, Simmons and Sytkowski, the ordinary artisan would have found motivation use the IgG4 Fc of Lilly in the construct of Andrews in view of Simmons and Sytkowski where according to Lilly the IgG4 Fc is preferable.

14. Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrews et al. (Gene 182:101-109 (1996); cited in the IDS of 1/5/10) in view of Simmons et al. (Nat. Biotech. 14:629-634 (1996)) and further in view of Sytkowski et al. (WO 99/02709; published 1/21/99); cited in the IDS of 10/9/09) as applied to claim 1 above, and further in view of Kwon et al. (WO200015661; published 3/23/00; cited in the PTO 892 form of 12/4/09).

Claim 11 is drawn to the heat stable enterotxin signal sequence of SEQ ID NO: 36, 37, 38, 40, 41, 42, 43, 44, 45, or 46.

Kwon teaches heat stable enterotoxin II signal sequence having 100% identity to SEQ ID NO: 36, 37, 38, 39, 40, 41, 42, 43, 44, 45 and 46 of Claim 11 (see attached sequence search alignments) and used to construct fusion proteins. Kwon teaches the modified signal sequences enhance the efficiency of peptide secretion from the E. coli cells, and the modified signal peptides may be used according to standard recombinant DNA methodologies to direct the secretion of peptides from microorganisms (Abstract). Thus in view of Andrews, Simmons and Sytkowski, the ordinary artisan would have found motivation to use the modified signal peptide sequences of Kwon in the construct of Andrews in view of Simmons and Sytkowski where the ordinary artisan would be reasonably assured that the signal peptides would have enhanced the secretion of Fc."

Conclusion

15. No claims are allowed.

16. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 1/5/10 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner, Art Unit 1643